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(54) Title: **ANTIGENIC POLYPEPTIDES**

(57) Abstract: The invention relates to a method for the identification of antigenic polypeptides expressed by pathogenic microbes; vaccines comprising said polypeptides; recombinant methods to manufacture said polypeptides; and therapeutic antibodies directed to said polypeptides.

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Antigenic Polypeptides

The invention relates to a method for the identification of antigenic polypeptides expressed by pathogenic microbes; vaccines comprising said polypeptides; 5 recombinant methods to manufacture said polypeptides; and therapeutic antibodies directed to said polypeptides.

Microbial organisms cause a number of fatal or debilitating diseases which affect many millions of people around the world. Currently methods to control microbial 10 organisms include the use of antimicrobial agents (antibiotics) and disinfectants. These have proved to be problematic since exposure to these agents places a significant selection pressure resulting in the creation of resistant microbes which can avoid the effects of the antimicrobial agent(s). For example, recently it has been discovered that microbial organisms have become resistant to triclosan, an agent 15 added to many disinfectants used in households and industrial environments.

An arguably greater problem is the evolution of antibiotic resistant strains of a number of significant pathogenic microbes.

20 For example, and not by way of limitation, it is estimated that there are up to 50 million people world-wide infected with drug resistant tuberculosis (TB) (Figures from the World Health Organisation, 1998). In the past the use of antibiotics to treat TB relied on the administration of single drugs (eg ethionamide) which promoted a relatively high frequency of resistance. For this reason, combinations of drugs are 25 now used to treat tuberculosis. However the fatality rate in cases caused by strains that are resistant to at least one drug used to treat tuberculosis still approaches 50% even when treatment is given. *Mycobacterium tuberculosis*, the causative agent of TB, is a slow growing bacteria and takes a long time to kill. Therefore, for a drug combination to be effective a person with TB must take the drug combination daily 30 for at least six months. Accordingly, patients frequently have to take two or more pills daily and this requires a regimented dosage over a relatively long period of

treatment. Many patients take the medications only intermittently and therefore do not finish the full course of therapy to completely eradicate the *M. tuberculosis* infection. Moreover, TB is strongly associated with HIV infection and therefore the establishment of TB is strongly correlated with immunosuppression.

5

Vaccination against TB has been available for many years. The bacillus calmette and guerin (BCG) vaccination has been widely used throughout the world for a long time because it is a safe and inexpensive means to vaccinate large numbers of people who potentially could contract TB. BCG is derived from live, attenuated strains of
10 *Mycobacterium bovis*. However the impact of vaccination on the infectious forms of TB is minimal and BCG has therefore contributed little to the overall control of the disease.

A further example of a pathogenic organism which has developed resistance to
15 antibiotics is *Staphylococcus aureus*. *S.aureus* is a bacterium whose normal habitat is the epithelial lining of the nose in about 20-40% of normal healthy people and is also commonly found on people's skin usually without causing harm. However, in certain circumstances, particularly when skin is damaged, this germ can cause infection. This is a particular problem in hospitals where patients may have surgical
20 procedures and/or be taking immunosuppressive drugs. These patients are much more vulnerable to infection with *S.aureus* because of the treatment they have received. Resistant strains of *S.aureus* have arisen in recent years. Methicillin resistant strains are prevalent and many of these resistant strains are also resistant to several other antibiotics. Currently there is no effective vaccination procedure for *S.*
25 *aureus*. In the US, *S.aureus* infections are the cause of 13% of the two million hospitalised infections each year. This represents 260,000 people with an infection of *S.aureus*, of which 60-80,000 die.

S. aureus is therefore a major human pathogen capable of causing a wide range of
30 life threatening diseases including septicaemia, endocarditis, arthritis and toxic shock. This ability is determined by the versatility of the organism and its arsenal of

components involved in virulence. Pathogenicity is multifactorial and no one component has shown to be responsible for a particular infection, see Projan, S.J. & Novick, R.P. (1997) in *The Staphylococci in Human Disease* (Crossley, K.B. & Archer, G.L., eds.) pp.55-81.

5

At the onset of infection, and as it progresses, the needs and environment of the organism changes and this is mirrored by a corresponding alteration in the virulence determinants which *S. aureus* produces. At the beginning of infection it is important for the pathogen to adhere to host tissues and so a large repertoire of cell surface associated attachment proteins are made. These include collagen-, fibrinogen- and fibronectin-binding proteins. The pathogen also has the ability to evade host defences by the production of factors that reduce phagocytosis or interfere with the ability of the cells to be recognised by circulating antibodies.

15 Often a focus of infection develops as an abscess and the number of organisms increases. *S. aureus* has the ability to monitor its own cell density by the production of a quorum sensing peptide. Accumulation of the peptide, associated with physiological changes brought about by the beginning of starvation of the cells, elicits a switch in virulence determinant production from adhesins to components involved in invasion and tissue penetration. These include a wide range of hemolysins, proteases and other degradative enzymes.

During the process of any infection the virulence determinants made by *S. aureus* are produced in response to environmental and physiological stimuli. These stimuli will be dependent on the niche within the body and will change as the infection progresses. Little is known of the conditions *in vivo* and it is likely that some components are produced solely in this environment. These are therefore potential vaccine components, which could not be discovered by previous techniques.

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One of the most important developments in recent medical history is the development of vaccines which provide prophylactic protection from a wide variety of pathogenic organisms. Many vaccines are produced by inactivated or attenuated pathogens which are injected into an individual. The immunised individual responds
5 by producing both a humoral (antibody) and cellular (cytolytic T cells, CTL's) response. For example, hepatitis vaccines are made by heat inactivating the virus and treating it with a cross linking agent such as formaldehyde. An example of an attenuated pathogen useful as a vaccine is represented by polio vaccines which are produced by attenuating a live pathogen.

10

However the use of attenuated organisms in vaccines for certain diseases is problematic due to the lack of knowledge regarding the pathology of the condition and the nature of the attenuation. For certain viral agents this is a particular problem since viruses, in particular retroviruses, have an error prone replication cycle which
15 results viable mutations in the genes which comprise the virus. This can result in alterations to antigenic determinants which have previously been used as vaccines. An alternative to the use of inactivated or attenuated pathogens is the identification of pathogen epitopes to which the immune system is particularly sensitive. In this regard many pathogenic toxins produced by pathogenic organisms during an
20 infection are particularly useful in the development of vaccines which protect the individual from a particular pathogenic organism.

The development of so-called subunit vaccines (vaccines in which the immunogen is a fragment or subunit of a protein or complex expressed by a particular pathogenic
25 organism) has been the focus of considerable medical research. The need to identify candidate molecules useful in the development of subunit vaccines is apparent not least because conventional chemotherapeutic approaches to the control of pathogenic organisms has more recently been stymied by the development of antibiotic resistance. A number of methods have been developed to identify potential antigenic
30 polypeptides which can be used as a vaccine. One such method is disclosed herein.

It has been known for many years that tumour cells produce a number of tumour cell specific antigens, some of which are presented at the tumour cell surface. The immune system recognises these antigens as foreign thereby resulting in the production of antibodies to self antigens, so called autoantibodies or autologous antisera.

One such technique is Serological identification of antigens by recombinant Expression Cloning, abbreviated to SEREX.

Typically, the technique involves the extraction of RNA from tumour tissue followed by the selective enrichment of mRNA from the isolated total RNA. The mRNA is reverse transcribed into cDNA using viral reverse transcriptase. The cDNA thus synthesised is subcloned into an expression vector and transformed into an appropriate bacterial strain. The transformed bacteria are plated onto a suitable nutrient agar and under appropriate growth conditions the subcloned cDNA is expressed from the expression vector in the bacterial cell. The cells are lysed naturally by the use of phage based expression vectors, for example λ phage or phagemid based vectors, which through their lytic cycle cause cell lysis. The released polypeptides are transferred to a suitable membrane support (i.e. nitrocellulose, nylon) and exposed to autologous antisera from the patient from which the tumour tissue was originally isolated. The immunoscreening methodology allows the identification of genes that are over expressed or inappropriately expressed in a selected tumour tissue from a patient.

We have exploited this technique to identify antigenic polypeptides expressed by pathogenic organisms during an infection. Autologous antisera produced during the infection is used to screen an expression library created from genomic DNA to identify and clone antigens.

In its broadest aspect the invention relates to the identification of antigenic polypeptides expressed during an infection by a pathogenic microbe.

According to a first aspect of the invention there is provided a method to identify
5 antigenic polypeptides comprising:

- (i) providing a nucleic acid library encoding genes or partial gene sequences of a pathogenic organism;
- 10 (ii) transforming/transfecting said library into a host cell;
- (iii) providing conditions conducive to the expression of said transformed/transfected genes or partial gene sequences;
- 15 (iv) contacting the polypeptides expressed by the genes/partial gene sequences with autologous antisera derived from an animal infected with, or has been infected with, said pathogenic organism; and
- (v) purifying the nucleic acid encoding the polypeptide or partial polypeptide
20 binding to said autologous antisera.

In a preferred method of the invention said library comprises genomic DNA of a pathogenic organism.

25 Ideally said pathogenic organism is bacterial.

More preferably still said bacterial organism is selected from the following:

Staphylococcus aureus; *Staphylococcus epidermidis*; *Enterococcus faecalis*;
Mycobacterium tuberculosis; *Streptococcus group B*; *Streptococcus pneumoniae*;
30 *Helicobacter pylori*; *Neisseria gonorrhea*; *Streptococcus group A*; *Borrelia*

burgdorferi; *Coccidioides immitis*; *Histoplasma sapsulatum*; *Neisseria meningitidis* type B; *Shigella flexneri*; *Escherichia coli*; *Haemophilus influenzae*.

Preferably still said pathogenic organism is of the genus *Staphylococcus spp.* Ideally
5 organism is *Staphylococcus aureus* or *Staphylococcus epidermidis*.

In a further preferred embodiment of the invention said nucleic acid library is a lambda library, ideally a lambda expression library.

10 According to a second aspect of the invention there is provided a nucleic acid molecule comprising a DNA sequence selected from:

- (i) the DNA sequence as represented in SEQ ID NO's 1 – 13;
- 15 (ii) DNA sequences which hybridise to the sequence presented in the SEQ ID No's 1-13 identified in (i) above which encode a polypeptide expressed by a pathogenic organism and
- (iii) DNA sequences which are degenerate as a result of the genetic code to the
20 DNA sequences defined in (i) and (ii).

In a yet still further preferred embodiment of the invention said nucleic acid molecule is genomic DNA.
25

In a preferred embodiment of the invention there is provided an isolated nucleic acid molecule which anneals under stringent hybridisation conditions to the sequences presented in SEQ ID NO's 1- 13.

30 Stringent hybridisation/washing conditions are well known in the art. For example, nucleic acid hybrids that are stable after washing in 0.1xSSC, 0.1% SDS at 60°C. It

is well known in the art that optimal hybridisation conditions can be calculated if the sequences of the nucleic acid is known. For example, hybridisation conditions can be determined by the GC content of the nucleic acid subject to hybridisation. Please see Sambrook *et al* (1989) Molecular Cloning; A Laboratory Approach. A common
5 formula for calculating the stringency conditions required to achieve hybridisation between nucleic acid molecules of a specified homology is:

$$T_m = 81.5^{\circ} \text{C} + 16.6 \text{ Log } [\text{Na}^+] + 0.41 [\% \text{ G} + \text{C}] - 0.63 (\% \text{ formamide}).$$

10 According to a third aspect of the invention there is provided at least one polypeptide identified by the method according to the invention.

In a preferred embodiment of the invention, said polypeptide is associated with infective pathogenicity of an organism according to any previous aspect or
15 embodiment of the invention.

More preferably still said polypeptide is at least one, or part of SEQ ID NO's: 14- 19.

According to a fourth aspect of the invention there is provided a nucleic acid
20 molecule characterised in that said nucleic acid molecule is part of a vector adapted to facilitate recombinant expression of the polypeptide encoded by said nucleic acid molecule.

In a preferred embodiment of the invention said vector is an expression vector
25 adapted for prokaryotic gene expression. Alternatively said expression vector is adapted for eukaryotic gene expression.

Typically said adaptation includes, by example and not by way of limitation, the provision of transcription control sequences (promoter sequences) which mediate cell
30 specific expression. These promoter sequences may be cell specific, inducible or constitutive.

- Promoter is an art recognised term and, for the sake of clarity, includes the following features which are provided by example only, and not by way of limitation. Enhancer elements are *cis* acting nucleic acid sequences often found 5' to the transcription initiation site of a gene (enhancers can also be found 3' to a gene sequence or even
- 5 located in intronic sequences and is therefore position independent). Enhancers function to increase the rate of transcription of the gene to which the enhancer is linked. Enhancer activity is responsive to *trans* acting transcription factors (polypeptides) which have been shown to bind specifically to enhancer elements. The binding/activity of transcription factors (please see Eukaryotic Transcription Factors,
- 10 by David S Latchman, Academic Press Ltd, San Diego) is responsive to a number of environmental cues which include, by example and not by way of limitation, intermediary metabolites (eg glucose, lipids), environmental effectors (eg light, heat,).
- 15 Promoter elements also include so called TATA box and RNA polymerase initiation selection (RIS) sequences which function to select a site of transcription initiation. These sequences also bind polypeptides which function, *inter alia*, to facilitate transcription initiation selection by RNA polymerase.
- 20 Adaptations also include the provision of selectable markers and autonomous replication sequences which both facilitate the maintenance of said vector in either the eukaryotic cell or prokaryotic host. Vectors which are maintained autonomously are referred to as episomal vectors.
- 25 Adaptations which facilitate the expression of vector encoded genes include the provision of transcription termination/polyadenylation sequences. This also includes the provision of internal ribosome entry sites (IRES) which function to maximise expression of vector encoded genes arranged in bicistronic or multi-cistronic expression cassettes.

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These adaptations are well known in the art. There is a significant amount of published literature with respect to expression vector construction and recombinant DNA techniques in general. Please see, Sambrook et al (1989) Molecular Cloning: A Laboratory Manual, Cold Spring Harbour Laboratory, Cold Spring Harbour, NY and
5 references therein; Marston, F (1987) DNA Cloning Techniques: A Practical Approach Vol III IRL Press, Oxford UK; DNA Cloning: F M Ausubel et al, Current Protocols in Molecular Biology, John Wiley & Sons, Inc.(1994).

10 According to yet a further aspect of the invention there is provided a method for the production of the polypeptides according to any previous aspect or embodiment of the invention comprising:

(i) providing a cell transformed/transfected with a vector according to the
15 invention;

(ii) growing said cell in conditions conducive to the manufacture of said polypeptides; and

20 (iii) purifying said polypeptide from said cell, or its growth environment.

In a preferred method of the invention said vector encodes, and thus said recombinant polypeptide is provided with, a secretion signal to facilitate purification of said polypeptide.

25

According to a fifth aspect of the invention there is provided a cell or cell-line transformed or transfected with the vector according to the invention.

In a preferred embodiment of the invention said cell is a prokaryotic cell.
30 Alternatively said cell is a eukaryotic cell selected from: fungal, insect, amphibian; mammalian; plant.

According to a yet further aspect of the invention there is provided a vaccine comprising at least one polypeptide according to the invention.

- 5 Ideally said vaccine further comprises a carrier and/or adjuvant.

The terms adjuvant and carrier are construed in the following manner. Some polypeptide or peptide antigens contain B-cell epitopes but no T cell epitopes. Immune responses can be greatly enhanced by the inclusion of a T cell epitope in the
10 polypeptide/peptide or by the conjugation of the polypeptide/peptide to an immunogenic carrier protein such as key hole limpet haemocyanin or tetanus toxoid which contain multiple T cell epitopes. The conjugate is taken up by antigen presenting cells, processed and presented by human leukocyte antigens (HLA's) class II molecules. This allows T cell help to be given by T cell's specific for carrier
15 derived epitopes to the B cell which is specific for the original antigenic polypeptide/peptide. This can lead to increase in antibody production, secretion and isotype switching.

An adjuvant is a substance or procedure which augments specific immune responses
20 to antigens by modulating the activity of immune cells. Examples of adjuvants include, by example only, agonsitic antibodies to co-stimulatory molecules, Freund's adjuvant, muramyl dipeptides, liposomes. An adjuvant is therefore an immunomodulator. A carrier is an immunogenic molecule which, when bound to a second molecule augments immune responses to the latter.

25

In yet a further aspect of the invention there is provided a method to immunise an animal against a pathogenic microbe comprising administering to said animal at least one polypeptide, or part thereof, according to the invention or the vaccine according to the invention.

30

In a preferred method of the invention said animal is human.

Preferably the vaccine, or antigenic polypeptide, can be delivered by direct injection either intravenously, intramuscularly, subcutaneously. Further still, the vaccine or antigenic polypeptide, may be taken orally.

Preferably the vaccine is against the bacterial species *Staphylococcus aureus*.

- 5 The vaccine may also be against the bacterial species *Staphylococcus epidermidis*.

It will also be apparent that vaccines or antigenic polypeptides are effective at preventing or alleviating conditions in animals other than humans, for example and not by way of limitation, family pets, livestock, horses.

- 10 According to a further aspect of the invention there is provided an antibody, or at least an effective binding part thereof, which binds at least one polypeptide according to the invention.

In a preferred embodiment of the invention said antibody is a polyclonal or monoclonal antibody wherein said antibody is specific to said polypeptide.

15

Alternatively, said antibody is a chimeric antibody produced by recombinant methods to contain the variable region of said antibody with an invariant or constant region of a human antibody.

- 20 In a further alternative embodiment of the invention, said antibody is humanised by recombinant methods to combine the complementarity determining regions of said antibody with both the constant (C) regions and the framework regions from the variable (V) regions of a human antibody.

- 25 Preferably said antibody is provided with a marker including a conventional label or tag, for example a radioactive and/or fluorescent and/or epitope label or tag.

Preferably said humanised monoclonal antibody to said polypeptide is produced as a fusion polypeptide in an expression vector suitably adapted for transfection or transformation of prokaryotic or eukaryotic cells.

Antibodies, also known as immunoglobulins, are protein molecules which have specificity for foreign molecules (antigens). Immunoglobulins (Ig) are a class of structurally related proteins consisting of two pairs of polypeptide chains, one pair of light (L) (low molecular weight) chain (κ or λ), and one pair of heavy (H) chains (γ , α , μ , δ and ϵ), all four linked together by disulphide bonds. Both H and L chains have regions that contribute to the binding of antigen and that are highly variable from one Ig molecule to another. In addition, H and L chains contain regions that are non-variable or constant.

10

The L chains consist of two domains. The carboxy-terminal domain is essentially identical among L chains of a given type and is referred to as the "constant" (C) region. The amino terminal domain varies from L chain to L chain and contributes to the binding site of the antibody. Because of its variability, it is referred to as the "variable" (V) region.

15

The H chains of Ig molecules are of several classes, α , μ , σ , α , and γ (of which there are several sub-classes). An assembled Ig molecule consisting of one or more units of two identical H and L chains, derives its name from the H chain that it possesses. Thus, there are five Ig isotypes: IgA, IgM, IgD, IgE and IgG (with four sub-classes based on the differences in the H chains, i.e., IgG1, IgG2, IgG3 and IgG4). Further detail regarding antibody structure and their various functions can be found in, Using Antibodies: A laboratory manual, Cold Spring Harbour Laboratory Press.

20

Chimeric antibodies are recombinant antibodies in which all of the V-regions of a mouse or rat antibody are combined with human antibody C-regions. Humanised antibodies are recombinant hybrid antibodies which fuse the complementarity determining regions from a rodent antibody V-region with the framework regions from the human antibody V-regions. The C-regions from the human antibody are also used. The complementarity determining regions (CDRs) are the regions within the N-terminal domain of both the heavy and light chain of the antibody to where the

25
30

majority of the variation of the V-region is restricted. These regions form loops at the surface of the antibody molecule. These loops provide the binding surface between the antibody and antigen.

- 5 Antibodies from non-human animals provoke an immune response to the foreign antibody and its removal from the circulation. Both chimeric and humanised antibodies have reduced antigenicity when injected to a human subject because there is a reduced amount of rodent (i.e. foreign) antibody within the recombinant hybrid antibody, while the human antibody regions do not illicit an immune response. This results in a weaker immune response and a decrease in the clearance of the antibody. This is clearly desirable when using therapeutic antibodies in the treatment of human diseases. Humanised antibodies are designed to have less "foreign" antibody regions and are therefore thought to be less immunogenic than chimeric antibodies.
- 10
- 15 In another aspect of the invention there is provided a vector which is adapted for the expression of the humanised or chimeric antibodies according to the invention.

- In a yet further aspect of the invention, there is provided a cell or cell line which has been transformed or transfected with the vector encoding the humanised or chimeric antibody according to the invention.
- 20

In a yet further aspect of the invention there is provided a method for the production of the humanised or chimeric antibody according to the invention comprising :

- (i) providing a cell transformed or transfected with a vector which comprises a nucleic acid molecule encoding the humanised or chimeric antibody according to the invention;
- 25
- (ii) growing said cell in conditions conducive to the manufacture of said antibody; and
- (iii) purifying said antibody from said cell, or its growth environment.

30

In a yet further aspect of the invention there is provided a hybridoma cell line which produces a monoclonal antibody as hereinbefore described.

5 In a further aspect of the invention there is provided a method of producing monoclonal antibodies according to the invention using hybridoma cell lines according to the invention.

In a further aspect of the invention there is provided a method for preparing a hybridoma cell-line producing monoclonal antibodies according to the invention
10 comprising the steps of:

- i) immunising an immunocompetent mammal with an immunogen comprising at least one polypeptide having the amino acid sequence as represented in SEQ. ID No 14-19, or fragments thereof;
- 15 ii) fusing lymphocytes of the immunised immunocompetent mammal with myeloma cells to form hybridoma cells;
- iii) screening monoclonal antibodies produced by the hybridoma cells of step (ii) for binding activity to the amino acid sequences of (i);
- iv) culturing the hybridoma cells to proliferate and/or to secrete said monoclonal antibody; and
- 20 v) recovering the monoclonal antibody from the culture supernatant.

Preferably, the said immunocompetent mammal is a mouse. Alternatively, said immunocompetent mammal is a rat.

25 The production of monoclonal antibodies using hybridoma cells is well-known in the art. The methods used to produce monoclonal antibodies are disclosed by Kohler and Milstein in Nature 256, 495-497 (1975) and also by Donillard and Hoffman, "Basic Facts about Hybridomas" in Compendium of Immunology V.II ed. by Schwartz, 1981, which are incorporated by reference.

30

In a further aspect of the invention there is provided the use of the antibodies for manufacture of a medicament for the treatment of *Staphylococcus aureus*-associated septicaemia, food-poisoning or skin disorders.

- 5 In another aspect of the invention there is provided the use of the antibodies according to the invention for the manufacture of a medicament for the treatment of *Staphylococcus epidermidis*-associated septicaemia, peritonitis or endocarditis.

- 10 It will be apparent that the polypeptides identified by the method according to the invention will facilitate the production of therapeutic antibodies to a range of diseases resulting from pathogenic infection, for example, septicaemia; tuberculosis; bacteria-associated food poisoning; blood infections; peritonitis; endocarditis; sepsis; meningitis; pneumonia; stomach ulcers; gonorrhoea; strep throat; streptococcal-associated toxic shock; necrotizing fasciitis; impetigo; histoplasmosis; Lyme disease;
15 gastro-enteritis; dysentery; shigellosis.

As has already been stated earlier, microbial organisms cause a wide variety of diseases. Listed below, and not by way of limitation, are a number of micro-organisms and some of the diseases they cause.

20

Micro-organism	Disease(s) caused
<i>Staphylococcus aureus</i>	Sepsis, food poisoning, septicaemia,
<i>Staphylococcus epidermidis</i>	Peritonitis, septicaemia, endocarditis, other hospital-associated diseases
<i>Enterococcus faecalis</i>	Endocarditis, cystitis, wound infections
<i>Mycobacterium tuberculosis</i>	Tuberculosis
<i>Streptococcus group B</i>	Sepsis, meningitis, pneumonia, bladder infections
<i>Streptococcus pneumoniae</i>	Pneumonia, meningitis
<i>Helicobacter pylori</i>	Stomach ulcers
<i>Neisseria gonorrhoea</i>	Gonorrhoea
<i>Streptococcus group A</i>	Strep throat, necrotizing fasciitis, impetigo, Strep. Toxic shock syndrome
<i>Borrelia burgdoferi</i>	Lyme disease
<i>Coccidiodes immitis</i>	Pneumonia

<i>Histoplasma sapsulatum</i>	Histoplasmosis, pneumonia
<i>Neisseria meningitidis type B</i>	Meningitis
<i>Shigella flexneri</i>	Gastro-enteritis, shigellosis, dysentery
<i>Escherichia coli</i>	Food-poisoning, gastro-enteritis
<i>Haemophilus influenzae</i>	Meningitis, pneumonia, arthritis, cellulitis

An embodiment of the invention will now be described by example only and with
 5 reference to the following materials, methods and SEQ ID NO's 1-19 and Table 1.

Materials and Methods

A λ ZAP Express library of genomic DNA of *S. aureus* 8325/4 was used. It contains
 10 fragments of 2-10kb from a partial *Sau*3A digest of total genomic DNA. This was
 cloned into the *Bam*HI site of the vector. The library contains >10x coverage of the
 genome. The library was probed by plaque lift using an initial screen of
 approximately 20,000 plaque forming units on a 9cm diameter Petri dish. The
 plating cells used, their treatment, the plating procedure and buffers were exactly as
 15 described in the manufacturers handbook (Stratagene). Plating cells, *Escherichia*
coli XL1-Blue MRF', were infected with phage and plated in 3 ml top LB agar
 containing 10 mM MgSO₄ onto LB plates containing 10 mM MgSO₄. The plates
 were then incubated at 42°C for 4 hr. An 8.5cm diameter nitrocellulose filter disc
 (previously soaked in 10 mM IPTG and air-dried) was placed on each plate and its
 20 location marked. The plates were then incubated for a further 3.5 hr at 37°C. The
 filters were removed and washed in TBST buffer before blocking overnight at 4°C in
 TBST containing 6% w/v dried skimmed milk and 3% v/v pig serum (Sigma). The
 serum was used to block any Protein A clones on the filter. The filters are then
 treated with patient serum (1/5000 dilution) in blocking solution for 90 min at room
 25 temperature. Antisera have been obtained from patients convalescing from major *S.*
aureus infections. The filters are then washed for 3x10 min in TBST. Secondary
 antibody used was goat anti-human whole IgG alkaline phosphatase linked (Sigma)

at 1/30,000 dilution in blocking solution at room temperature for 30 min. The filters were then washed as above and developed using a standard colorimetric procedure.

5 Cross-reactive plaques were located on the agar plates and cored into 0.2ml phage buffer with 0.02 ml chloroform. The titre of each core stock was determined and the phage plated at approximately 200 plaques per plate. A plaque lift and screen was performed as above to give single, pure cross-reactive clones.

10 The pure clones were then spotted (1µl) onto plates to give a confluent plaque of 0.5cm diameter. 30 individual clones can be spotted on each plate. A plaque lift is performed and the filter probed with an appropriate sera. In this way clones can be tested for their cross-reactivity with other patient sera, non-infected donor sera and anti-Protein A sera.

15 Individual clones were then excised to give a phagemid in *E. coli* XL0LR using the manufacturers protocol (Stratagene). A plasmid miniprep of each was carried out and the size of the genomic insert determined by restriction mapping. The identity of the cloned insert was determined by DNA sequencing using primers against vector sequence, which allows sequencing across the insert. By comparison of the derived
20 sequence against the public domain databases the nature of the cloned gene(s) can be determined.

Hybridisation Solutions/Conditions

25 Typically, hybridisation conditions uses 4 – 6 x SSPE (20x SSPE contains 175.3g NaCl, 88.2g NaH₂PO₄ H₂O and 7.4g EDTA dissolved to 1 litre and the pH adjusted to 7.4); 5-10x Denhardts solution (50x Denhardts solution contains 5g Ficoll (type 400, Pharmacia), 5g polyvinylpyrrolidone abd 5g bovine serum albumen; 100µg-
1.0mg/ml sonicated salmon/herring DNA; 0.1-1.0% sodium dodecyl sulphate;
30 optionally 40-60% deionised formamide. Hybridisation temperature will vary

depending on the GC content of the nucleic acid target sequence but will typically be between 42⁰- 65⁰ C.

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10

Staphylococcus aureus clones identified in human sera screen

TABLE 1

Patient Sera	Clone	Encoded proteins	Locus number
A	1	γ hemolysin B and C subunit	1
A	3	Atl	2
A	4	γ hemolysin B and C subunit	1
A	5	γ hemolysin B and C subunit	1
A	7	Novel putative protease (ORF1 novel antigen like)	7
A	8	Novel nuclease (YisK)	5
A	9	Novel autolysin	6
A	10	γ hemolysin B and C subunit	1
A	11	Atl	2
A	14	γ hemolysin B and C subunit	1
A	15	γ hemolysin B and C subunit	1
A	S1	Novel putative protease (ORF1 novel antigen like)	7
A	S5	Novel surface protein	12
A	S17	γ hemolysin B and C subunit	1
A	S18	Novel putative protease (ORF1 novel antigen like)	7
A	S19	Novel autolysin	6
A	S20	Novel surface protein/toxin	13
A	S21	γ hemolysin B and C subunit	1
A	S25	γ hemolysin B and C subunit	1
A	S29	Fibrinogen binding protein)	3
A	S44	Novel surface protein	12
A	S45	Atl	2
A	S55	Atl	2
A	S64	Atl	2
A	S66	Atl	2
B	2	Novel exotoxin (exotoxin 2 like)	8
C	1	Coagulase	4
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C	3	Coagulase	4
C	4	Coagulase	4
C	5	Coagulase	4
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C	14	Coagulase	4
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C	19	Coagulase	4
C	20	Coagulase	4
C	25	Coagulase	4
E	6	Novel surface proteins	9/10
E	7	Novel surface proteins	9/10
E	11	γ hemolysin B and C subunit	1
F	1	Novel exotoxin (exotoxin 2 like)	8
F	2	Novel exotoxin (exotoxin 2 like)	8
F	3	Novel exotoxin (exotoxin 2 like)	8
F	4	Novel exotoxin (exotoxin 2 like)	8
F	5	Novel hemolysin (Yjfd)	11

CLAIMS

1. An isolated nucleic acid molecule comprising a DNA sequence selected from
5 the group consisting of:

(i) the DNA sequence as represented in SEQ ID NO's 1 – 13;

10 (ii) DNA sequences which hybridise to the sequence presented in the SEQ
ID No's 1-13 identified in (i) above and which encode a polypeptide
expressed by a pathogenic organism; and

(iii) DNA sequences which are degenerate as a result of the genetic code to
the DNA sequences defined in (i) and (ii).

15

2. An isolated nucleic acid molecule according to claim 1 which is genomic
DNA.

20 3. An isolated nucleic acid molecule according to claim 1 or 2 which anneals
under stringent hybridisation conditions to the sequences presented in SEQ ID
NO's 1-13.

4. A vector comprising a nucleic acid molecule according to any of claims 1-3.

25 5. A vector according to claim 4 wherein the vector is adapted for recombinant
expression of the polypeptide encoded by the nucleic acid.

6. A vector according to claim 4 or 5 wherein said vector is an expression vector
adapted for prokaryotic gene expression.

30

7. A vector according to claim 4 or 5 wherein said vector is an expression
vector adapted for eukaryotic gene expression.

8. A vector according to any of claims 4 to 7 wherein the adaptation of the vector includes the provision of promoter sequences.
- 5 9. A vector according to claim 8 wherein the promoter sequences provide for cell specific, inducible or constitutive expression.
10. A method to identify antigenic polypeptides comprising:
- 10 (i) providing a nucleic acid library encoding genes or partial gene sequences of a pathogenic organism;
- (ii) transforming/transfecting said library into a host cell;
- 15 (iii) contacting the polypeptides expressed by the genes/partial gene sequences with autologous antisera derived from an animal infected with, or has been infected with, said pathogenic organism; and
- (iv) purifying the nucleic acid encoding the polypeptide or partial polypeptide
20 binding to said autologous antisera.
11. A method according to claim 10 wherein said library comprises genomic DNA of a pathogenic organism.
- 25 12. A method according to claim 10 or claim 11 wherein said pathogenic organism is bacterial.
13. A method according to any of claims 10 to 12 wherein said bacterial organism is selected from the following: *Staphylococcus aureus*; *Staphylococcus epidermidis*; *Enterococcus faecalis*; *Mycobacterium tuberculosis*; *Streptococcus group B*; *Streptococcus pneumoniae*; *Helicobacter pylori*;
- 30

Neisseria gonorrhea; *Streptococcus* group A; *Borrelia burgdorferi*;
Coccidioides immitis; *Histoplasma sapsulatum*; *Neisseria meningitidis* type B;
Shigella flexneri; *Escherichia coli*; *Haemophilus influenzae*

- 5 14. A method according to any of claim 13 wherein said pathogenic organism is
Staphylococcus aureus.
15. A method according to any of claim 13 wherein said pathogenic organism is
Staphylococcus epidermidis.
- 10 16. A method according to any of claims 10 to 15 wherein said nucleic acid
library is a lambda library.
17. A polypeptide identified by the method according to any of claims 10 to 16.
- 15 18. A polypeptide according to claim 17 which is selected from the group
consisting of SEQ ID NO's: 14-19.
19. A method for the production of the polypeptides according to any of claims
20 17 or 18 comprising:
- (i) providing a cell transformed/transfected with a vector according to
any of claims 4 to 9 and with cell culture conditions; and
- (ii) purifying said polypeptide from said cell, or its growth environment.
- 25 20. A method according to claim 19 wherein said vector encodes, and thus said
recombinant polypeptide is provided with, a secretion signal to facilitate
purification of said polypeptide.
21. A cell transformed or transfected with the vector according to any of claims 4
30 to 9.

22. A cell according to claim 21 which is a prokaryotic cell.
23. A cell according to claim 21 which is a eukaryotic cell selected from the
group consisting of: fungal cell, insect cell, amphibian cell; mammalian cell;
5 plant cell.
24. A vaccine comprising at least one polypeptide according to claims 16 or 17.
25. A vaccine according to claim 24 which further comprises a carrier and/or
10 adjuvant.
26. A method to immunise an animal against a pathogenic microbe comprising
administering to the animal at least one polypeptide, or part thereof, according
to any previous claim or the vaccine of any previous claim.
- 15 27. A method according to claim 26 wherein the animal is human.
28. A method according to claim 26 or 27 wherein the vaccine, or antigenic
polypeptide, is delivered by direct injection either intravenously, intramuscularly or
20 subcutaneously.
29. A method according to claim 25 or 26 wherein the vaccine or antigenic
polypeptide is taken orally.
30. A method according to any of claims 26 to 29 wherein the vaccine is against
the bacterial genus *Staphylococcus spp.*
- 25 31. A method according to claim 30 wherein the vaccine is against the bacterial
species *Staphylococcus aureus*.
32. A method according to claim 30 wherein the vaccine is against the bacterial
species *Staphylococcus epidermidis*.

33. An antibody, or at least an effective part thereof, which binds at least with a selective part of the polypeptide according to claim 16 or 17.
34. An antibody according to claim 33 which is a monoclonal antibody.
- 5 35. An antibody according to claim 33 or 34 wherein said effective part comprises FAb fragments.
36. An antibody according to any of claims 33 to 35 which is a chimeric
10 antibody.
37. An antibody according to any of claims 33 to 35 which is a humanised antibody.
- 15 38. An antibody according to any of claims 33 to 37 wherein said antibody is provided with a marker, label or tag.
39. An antibody according to claim 38 wherein said antibody is provided with a marker selected from a group consisting of: a radioactive label, a fluorescent
20 label; an epitope tag.
40. An antibody according to any of claims 34 to 39 which is produced as a fusion polypeptide.
- 25 41. A vector which is adapted for the expression of the antibodies according to any of claims 34-40.
42. A cell which has been transformed or transfected with the vector according to claim 41.
- 30

43. A method for the production of the antibody according to any of claims 34 or 40 comprising :
- 5 i) providing a cell transformed or transfected with the vector according to claim 41 and with cell culture conditions; and
- ii) purifying said antibody from said cell, or its growth environment.
44. A hybridoma cell line which produces an antibody according to claim 34.
45. Use of the antibodies according to any of claims 33 to 40 for the manufacture
10 of a medicament for the treatment of *Staphylococcus aureus*-associated septicaemia, food-poisoning or skin disorders.
46. Use of the antibodies according to any of claims 33 to 40 for the manufacture
15 of a medicament for the treatment of *Staphylococcus epidermidis*-associated septicaemia, peritonitis or endocarditis
47. A method for preparing a hybridoma cell-line producing monoclonal antibodies according to claim 34, comprising the steps of:
- 20 i) immunising an immunocompetent mammal with an immunogen comprising at least one polypeptide having the amino acid sequence as set forward in SEQ ID No: 14-19, or fragments thereof;
- ii) fusing lymphocytes of the immunised immunocompetent mammal with myeloma cells to form hybridoma cells;
- iii) screening monoclonal antibodies produced by the hybridoma cells of
25 step (ii) for binding activity to the amino acid sequences of (i);
- iv) culturing the hybridoma cells to proliferate and/or to secrete said monoclonal antibody; and
- v) recovering the monoclonal antibody from the culture supernatant.
- 30 48. A method according to claim 47, wherein said immunocompetent mammal is a mouse

49. A method according to claim 47, wherein said immunocompetent mammal is
a rat

5

10

SEQUENCE LISTING

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Ile Lys Met Gly Lys Val Ala Pro Trp Gly Thr Gln Ser Thr Thr Thr
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30 Pro Thr Thr Pro Ser Lys Pro Thr Thr Pro Ser Lys Pro Ser Thr Gly
 130 135 140

Lys Leu Thr Val Ala Ala Asn Asn Gly Val Ala Gln Ile Lys Pro Thr
 145 150 155 160

35 Asn Ser Gly Leu Tyr Thr Thr Val Tyr Asp Lys Thr Gly Lys Ala Thr
 165 170 175

40 Asn Glu Val Gln Lys Thr Phe Ala Val Ser Lys Thr Ala Thr Leu Gly
 180 185 190

Asn Gln Lys Phe Tyr Leu Val Gln Asp Tyr Asn Ser Gly Asn Lys Phe
 195 200 205

45 Gly Trp Val Lys Glu Gly Asp Val Val Tyr Asn Thr Ala Lys Ser Pro
 210 215 220

Val Asn Val Asn Gln Ser Tyr Ser Ile Lys Pro Gly Thr Lys Leu Tyr
 225 230 235 240

50 Thr Val Pro Trp Gly Thr Ser Lys Gln Val Ala Gly Ser Val Ser Gly
 245 250 255

55 Ser Gly Asn Gln Thr Phe Lys Ala Ser Lys Gln Gln Gln Ile Asp Lys
 260 265 270

Ser Ile Tyr Leu Tyr Gly Ser Val Asn Gly Lys Ser Gly Trp Val Ser
 275 280 285

60 Lys Ala Tyr Leu Val Asp Thr Ala Lys Pro Thr Pro Thr Pro Thr Pro
 290 295 300

Lys Pro Ser Thr Pro Thr Thr Asn Asn Lys Leu Thr Val Ser Ser Leu

	305		310		315		320
	Asn Gly Val Ala	Gln Ile Asn Ala Lys	Asn Asn Gly Leu Phe Thr Thr				
		325	330				335
5	Val Tyr Asp Lys	Thr Gly Lys Pro Thr Lys Glu Val Gln Lys Thr Phe					
		340	345				350
10	Ala Val Thr Lys	Glu Ala Ser Leu Gly Gly Asn Lys Phe Tyr Leu Val					
		355	360				365
	Lys Asp Tyr Asn Ser Pro	Thr Leu Ile Gly Trp Val Lys Gln Gly Asp					
		370	375				380
15	Val Ile Tyr Asn Asn Ala	Lys Ser Pro Val Asn Val Met Gln Thr Tyr					
		385	390				395
	Thr Val Lys Pro	Gly Thr Lys Leu Tyr Ser Val Pro Trp Gly Thr Tyr					
		405	410				415
20	Lys Gln Glu Ala	Gly Ala Val Ser Gly Thr Gly Asn Gln Thr Phe Lys					
		420	425				430
25	Ala Thr Lys Gln Gln Gln Ile	Asp Lys Ser Ile Tyr Leu Phe Gly Thr					
		435	440				445
	Val Asn Gly Lys Ser Gly Trp	Val Ser Lys Ala Tyr Leu Ala Val Pro					
		450	455				460
30	Ala Ala Pro Lys Lys Ala	Val Ala Gln Pro Lys Thr Ala Val Lys Ala					
		465	470				475
	Tyr Thr Val Thr	Lys Pro Gln Thr Thr Gln Thr Val Ser Lys Ile Ala					
		485	490				495
35	Gln Val Lys Pro	Asn Asn Thr Gly Ile Arg Ala Ser Val Tyr Glu Lys					
		500	505				510
40	Thr Ala Lys Asn Gly Ala	Lys Tyr Ala Asp Arg Thr Phe Tyr Val Thr					
		515	520				525
	Lys Glu Arg Ala His Gly	Asn Glu Thr Tyr Val Leu Leu Asn Asn Thr					
		530	535				540
45	Ser His Asn Ile Pro Leu	Gly Trp Phe Asn Val Lys Asp Leu Asn Val					
		545	550				555
	Gln Asn Leu Gly Lys Glu	Val Lys Thr Thr Gln Lys Tyr Thr Val Asn					
		565	570				575
50	Lys Ser Asn Asn Gly Leu	Ser Met Val Pro Trp Gly Thr Lys Asn Gln					
		580	585				590
55	Val Ile Leu Thr Gly Asn	Asn Ile Ala Gln Gly Thr Phe Asn Ala Thr					
		595	600				605
	Lys Gln Val Ser Val Gly	Lys Asp Val Tyr Leu Tyr Gly Thr Ile Asn					
		610	615				620
60	Asn Arg Thr Gly Trp Val	Asn Ala Lys Asp Leu Thr Ala Pro Thr Ala					
		625	630				635
	Val Lys Pro Thr Thr Ser	Ala Ala Lys Asp Tyr Asn Tyr Thr Tyr Val					

	645	650	655
	Ile Lys Asn Gly Asn Gly Tyr Tyr Tyr Val Thr Pro Asn Ser Asp Thr		
	660	665	670
5	Ala Lys Tyr Ser Leu Lys Ala Phe Asn Glu Gln Pro Phe Ala Val Val		
	675	680	685
10	Lys Glu Gln Val Ile Asn Gly Gln Thr Trp Tyr Tyr Gly Lys Leu Ser		
	690	695	700
	Asn Gly Lys Leu Ala Trp Ile Lys Ser Thr Asp Leu Ala Lys Glu Leu		
	705	710	715
15	Ile Lys Tyr Asn Gln Thr Gly Met Ala Leu Asn Gln Val Ala Gln Ile		
	725	730	735
	Gln Ala Gly Leu Gln Tyr Lys Pro Gln Val Gln Arg Val Pro Gly Lys		
	740	745	750
20	Trp Thr Gly Ala Asn Phe Asn Asp Val Lys His Ala Met Asp Thr Lys		
	755	760	765
25	Arg Leu Ala Gln Asp Pro Ala Leu Lys Tyr Gln Phe Leu Arg Leu Asp		
	770	775	780
	Gln Pro Gln Asn Ile Ser Ile Asp Lys Ile Asn Gln Phe Leu Lys Gly		
	785	790	795
30	Lys Gly Val Leu Glu Asn Gln Gly Ala Ala Phe Asn Lys Ala Ala Gln		
	805	810	815
	Met Tyr Gly Ile Asn Glu Val Tyr Leu Ile Ser His Ala Leu Leu Glu		
	820	825	830
35	Thr Gly Asn Gly Thr Ser Gln Leu Ala Lys Gly Ala Asp Val Val Asn		
	835	840	845
40	Asn Lys Val Val Thr Asn Ser Asn Thr Lys Tyr His Asn Val Phe Gly		
	850	855	860
	Ile Ala Ala Tyr Asp Asn Asp Pro Leu Arg Glu Gly Ile Lys Tyr Ala		
	865	870	875
45	Lys Gln Ala Gly Trp Asp Thr Val Ser Lys Ala Ile Val Gly Gly Ala		
	885	890	895
	Lys Phe Ile Gly Asn Ser Tyr Val Lys Ala Gly Gln Asn Thr Leu Tyr		
	900	905	910
50	Lys Met Arg Trp Asn Pro Ala His Pro Gly Thr His Gln Tyr Ala Thr		
	915	920	925
55	Asp Val Asp Trp Ala Asn Ile Asn Ala Lys Ile Ile Lys Gly Tyr Tyr		
	930	935	940
	Asp Lys Ile Gly Glu Val Gly Lys Tyr Phe Asp Ile Pro Gln Tyr Lys		
	945	950	955
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<210> 16
 <211> 386
 <212> PRT
 <213> Staphylococcus aureus

5

<400> 16
 Asp Gln Tyr Ser Glu Asp Ala Lys Lys Thr Gln Lys Asp Tyr Ala Ser
 1 5 10 15

10

Gln Ser Lys Lys Asp Lys Asn Glu Lys Ser Asn Thr Lys Asn Pro Gln
 20 25 30

Leu Pro Thr Gln Asp Glu Leu Lys His Lys Ser Lys Pro Ala Gln Ser
 35 40 45

15

Phe Asn Asn Asp Val Asn Gln Lys Asp Thr Arg Ala Thr Ser Leu Phe
 50 55 60

20

Glu Thr Asp Pro Ser Ile Ser Asn Asn Asp Asp Ser Gly Gln Phe Asn
 65 70 75 80

Val Val Asp Ser Lys Asp Thr Arg Gln Phe Val Lys Ser Ile Ala Lys
 85 90 95

25

Asp Ala His Arg Ile Gly Gln Asp Asn Asp Ile Tyr Ala Ser Val Met
 100 105 110

Ile Ala Gln Ala Ile Leu Glu Ser Asp Ser Gly Arg Ser Ala Leu Ala
 115 120 125

30

Lys Ser Pro Asn His Asn Leu Phe Gly Ile Lys Gly Ala Phe Glu Gly
 130 135 140

35

Asn Ser Val Pro Phe Asn Thr Leu Glu Ala Asp Gly Asn Gln Leu Tyr
 145 150 155 160

Ser Ile Asn Ala Gly Phe Arg Lys Tyr Pro Ser Thr Lys Glu Ser Leu
 165 170 175

40

Lys Asp Tyr Ser Asp Leu Ile Lys Asn Gly Ile Asp Gly Asn Arg Thr
 180 185 190

Ile Tyr Lys Pro Thr Trp Lys Ser Glu Ala Asp Ser Tyr Lys Asp Ala
 195 200 205

45

Thr Ser His Leu Ser Lys Thr Tyr Ala Thr Asp Pro Asn Tyr Ala Lys
 210 215 220

50

Lys Leu Asn Ser Ile Ile Lys His Tyr Gln Leu Thr Gln Phe Asp Asp
 225 230 235 240

Glu Arg Met Pro Asp Leu Asp Lys Tyr Glu Arg Ser Ile Lys Asp Tyr
 245 250 255

55

Asp Asp Ser Ser Asp Glu Phe Lys Pro Phe Arg Glu Val Ser Asp Ser
 260 265 270

Met Pro Tyr Pro His Gly Gln Cys Thr Trp Tyr Val Tyr Asn Arg Met
 275 280 285

60

Lys Gln Phe Gly Thr Ser Ile Ser Gly Asp Leu Gly Asp Ala His Asn
 290 295 300

Trp Asn Asn Arg Ala Gln Tyr Arg Asp Tyr Gln Val Ser His Thr Pro
 305 310 315 320
 5 Lys Arg His Ala Ala Val Val Phe Glu Ala Gly Gln Phe Gly Ala Asp
 325 330 335
 Gln His Tyr Gly His Val Ala Phe Val Glu Lys Val Asn Ser Asp Gly
 340 345 350
 10 Ser Ile Val Ile Ser Glu Ser Asn Val Lys Gly Leu Gly Ile Ile Ser
 355 360 365
 His Arg Thr Ile Asn Ala Ala Ala Glu Glu Leu Ser Tyr Ile Thr
 370 375 380
 15 Gly Lys
 385
 20 <210> 17
 <211> 325
 <212> PRT
 <213> Staphylococcus aureus
 25 <400> 17
 Met Lys Met Asn Lys Leu Val Lys Ser Ser Val Ala Thr Ser Met Ala
 1 5 10 15
 30 Leu Leu Leu Leu Ser Gly Thr Ala Asn Ala Glu Gly Lys Ile Thr Pro
 20 25 30
 Val Ser Val Lys Lys Val Asp Asp Lys Val Thr Leu Tyr Lys Thr Thr
 35 35 40 45
 35 Ala Thr Ala Asp Ser Asp Lys Phe Lys Ile Ser Gln Ile Leu Thr Phe
 50 55 60
 Asn Phe Ile Lys Asp Lys Ser Tyr Asp Lys Asp Thr Leu Val Leu Lys
 65 70 75 80
 40 Ala Thr Gly Asn Ile Asn Ser Gly Phe Val Lys Pro Asn Pro Asn Asp
 85 90 95
 45 Tyr Asp Phe Ser Lys Leu Tyr Trp Gly Ala Lys Tyr Asn Val Ser Ile
 100 105 110
 Ser Ser Gln Ser Asn Asp Ser Val Asn Val Val Asp Tyr Ala Pro Lys
 115 120 125
 50 Asn Gln Asn Glu Glu Phe Gln Val Gln Asn Thr Leu Gly Tyr Thr Phe
 130 135 140
 Gly Gly Asp Ile Ser Ile Ser Asn Gly Leu Ser Gly Gly Leu Asn Gly
 145 150 155 160
 55 Asn Thr Ala Phe Ser Glu Thr Ile Asn Tyr Lys Gln Glu Ser Tyr Arg
 165 170 175
 60 Thr Thr Leu Ser Arg Asn Thr Asn Tyr Lys Asn Val Gly Trp Gly Val
 180 185 190
 Glu Ala His Lys Ile Met Asn Asn Gly Trp Gly Pro Tyr Gly Arg Asp
 195 200 205

Ser Phe His Pro Thr Tyr Gly Asn Glu Leu Phe Leu Ala Gly Arg Gln
 210 215 220
 5 Ser Ser Ala Tyr Ala Gly Gln Asn Phe Ile Ala Gln His Gln Met Pro
 225 230 235 240
 Leu Leu Ser Arg Ser Asn Phe Asn Pro Glu Phe Leu Ser Val Leu Ser
 245 250 255
 10 His Arg Gln Asp Gly Ala Lys Lys Ser Lys Ile Thr Val Thr Tyr Gln
 260 265 270
 Arg Glu Met Asp Leu Tyr Gln Ile Arg Trp Asn Gly Phe Tyr Trp Ala
 275 280 285
 15 Gly Ala Asn Tyr Lys Asn Phe Lys Thr Arg Thr Phe Lys Ser Thr Tyr
 290 295 300
 20 Glu Ile Asp Trp Glu Asn His Lys Val Lys Leu Leu Asp Thr Lys Glu
 305 310 315 320
 Thr Glu Asn Asn Lys
 325
 25
 <210> 18
 <211> 157
 <212> PRT
 30 <213> Staphylococcus aureus
 <400> 18
 Ser Phe Asn Tyr Ser Lys Ser Ile Ser Tyr Thr Gln Gln Asn Tyr Val
 1 5 10 15
 35 Ser Glu Val Glu Gln Gln Asn Ser Lys Ser Val Leu Trp Gly Val Lys
 20 25 30
 40 Ala Asn Ser Phe Ala Thr Glu Ser Gly Gln Lys Ser Ala Phe Asp Ser
 35 40 45
 Asp Leu Phe Val Gly Tyr Lys Pro His Ser Lys Asp Pro Arg Asp Tyr
 50 55 60
 45 Phe Val Pro Asp Ser Glu Leu Pro Pro Leu Val Gln Ser Gly Phe Asn
 65 70 75 80
 Pro Ser Phe Ile Ala Thr Val Ser His Glu Lys Gly Ser Ser Asp Thr
 85 90 95
 50 Ser Glu Phe Glu Ile Thr Tyr Gly Arg Asn Met Asp Val Thr His Ala
 100 105 110
 55 Ile Lys Arg Ser Thr His Tyr Gly Asn Ser Tyr Leu Asp Gly His Arg
 115 120 125
 Val His Asn Ala Phe Val Asn Arg Asn Tyr Thr Val Lys Tyr Glu Val
 130 135 140
 60 Asn Trp Lys Thr His Glu Ile Lys Val Lys Gly Gln Asn
 145 150 155

<210> 19
 <211> 345
 <212> PRT
 <213> Staphylococcus aureus

5

<400> 19
 Ile Ile Ala Ile Ile Ile Leu Ile Phe Ile Ser Phe Phe Phe Ser Gly
 1 5 10 15

10

Ser Glu Thr Ala Leu Thr Ala Ala Asn Lys Ala Lys Phe Lys Thr Glu
 20 25 30

Ala Asp Lys Gly Asp Lys Lys Ala Lys Gly Ile Val Lys Leu Leu Glu
 35 40 45

15

Lys Pro Ser Glu Phe Ile Thr Thr Ile Leu Ile Gly Asn Asn Val Ala
 50 55 60

20

Asn Ile Leu Leu Pro Thr Leu Val Thr Ile Met Ala Leu Arg Trp Gly
 65 70 75 80

Ile Ser Val Gly Ile Ala Ser Ala Val Leu Thr Val Val Ile Ile Leu
 85 90 95

25

Ile Ser Glu Val Ile Pro Lys Ser Val Ala Ala Thr Phe Pro Asp Lys
 100 105 110

Ile Thr Arg Leu Val Tyr Pro Ile Ile Asn Ile Cys Val Ile Val Phe
 115 120 125

30

Arg Pro Ile Thr Leu Leu Leu Asn Lys Leu Thr Asp Ser Ile Asn Arg
 130 135 140

Ser Leu Ser Lys Gly Gln Pro Gln Glu His Gln Phe Ser Lys Glu Glu
 145 150 155 160

35

Phe Lys Thr Met Leu Ala Ile Ala Gly His Glu Gly Ala Leu Asn Glu
 165' 170 175

40

Ile Glu Thr Ser Arg Leu Glu Gly Val Ile Asn Phe Glu Asn Leu Lys
 180 185 190

Val Lys Asp Val Asp Thr Thr Pro Arg Ile Asn Val Thr Ala Phe Ala
 195 200 205

45

Ser Asn Ala Thr Tyr Glu Glu Val Tyr Glu Thr Val Met Asn Lys Pro
 210 215 220

50

Tyr Thr Arg Tyr Pro Val Tyr Glu Gly Asp Ile Asp Asn Ile Ile Gly
 225 230 235 240

Val Phe His Ser Lys Tyr Leu Leu Ala Trp Ser Asn Lys Lys Glu Asn
 245 250 255

55

Gln Ile Thr Asn Tyr Ser Ala Lys Pro Leu Phe Val Asn Glu His Asn
 260 265 270

Lys Ala Glu Trp Val Leu Arg Lys Met Thr Ile Ser Arg Lys His Leu
 275 280 285

60

Ala Ile Val Leu Asp Glu Phe Gly Gly Thr Glu Ala Ile Val Ser His
 290 295 300

Glu Asp Leu Ile Glu Glu Leu Leu Gly Met Glu Ile Glu Asp Glu Met
 305 310 315 320
 5 Asp Lys Lys Glu Lys Glu Lys Leu Ser Gln Gln Gln Ile Gln Phe Gln
 325 330 335
 Gln Arg Lys Asn Arg Asn Val Ser Ile
 340 345
 10 <210> 20
 <211> 133
 <212> PRT
 <213> Staphylococcus aureus
 15 <400> 20
 Met Asn Lys Gln Gln Lys Glu Phe Lys Ser Phe Tyr Ser Ile Arg Lys
 1 5 10 15
 20 Ser Ser Leu Gly Val Ala Ser Val Ala Ile Ser Thr Leu Leu Leu Leu
 20 25 30
 Met Ser Asn Gly Glu Ala Gln Ala Ala Glu Glu Thr Gly Gly Thr
 35 40 45
 25 Asn Thr Glu Ala Gln Pro Lys Thr Glu Ala Val Ala Ser Pro Thr Thr
 50 55 60
 30 Thr Ser Glu Lys Ala Pro Glu Thr Lys Pro Val Ala Asn Ala Val Ser
 65 70 75 80
 Val Ser Asn Lys Glu Val Glu Ala Pro Thr Ser Glu Thr Lys Glu Ala
 85 90 95
 35 Lys Glu Val Lys Glu Val Lys Ala Pro Lys Glu Thr Lys Glu Val Lys
 100 105 110
 Pro Ala Ala Lys Ala Thr Asn Asn Thr Tyr Pro Ile Leu Asn Gln Glu
 115 120 125
 40 Leu Ile Arg Ser Asp
 130
 45 <210> 21
 <211> 205
 <212> PRT
 <213> Staphylococcus aureus
 50 <400> 21
 Asp His Gly Ile Val Phe Asn Ala Ser Leu Pro Leu Tyr Lys Asp Ala
 1 5 10 15
 55 Ile His Gln Lys Gly Ser Met Arg Ser Asn Asp Asn Gly Asp Asp Met
 20 25 30
 Ser Met Met Val Gly Thr Val Leu Ser Gly Phe Glu Tyr Arg Ala Gln
 35 40 45
 60 Lys Glu Lys Tyr Asp Asn Leu Tyr Lys Phe Phe Lys Glu Asn Glu Lys
 50 55 60
 Lys Tyr Gln Tyr Thr Gly Phe Thr Lys Glu Ala Ile Asn Lys Thr Gln

	65		70		75		80									
	Asn	Val	Gly	Tyr	Lys	Asn	Glu	Tyr	Phe	Tyr	Ile	Thr	Tyr	Ser	Ser	Arg
					85					90					95	
5	Ser	Leu	Lys	Glu	Tyr	Arg	Lys	Tyr	Tyr	Glu	Pro	Leu	Ile	Arg	Lys	Asn
				100					105					110		
10	Asp	Lys	Glu	Phe	Lys	Glu	Gly	Met	Glu	Arg	Ala	Arg	Lys	Glu	Val	Asn
			115					120					125			
	Tyr	Ala	Ala	Asn	Thr	Asp	Ala	Val	Ala	Thr	Leu	Phe	Ser	Thr	Lys	Lys
		130					135					140				
15	Asn	Phe	Thr	Lys	Asp	Asn	Thr	Val	Asp	Asp	Val	Ile	Glu	Leu	Ser	Asp
	145					150					155					160
	Lys	Leu	Tyr	Asn	Leu	Lys	Asn	Lys	Pro	Asp	Lys	Ser	Thr	Ile	Thr	Ile
				165						170					175	
20	Gln	Ile	Gly	Lys	Pro	Thr	Ile	Asn	Thr	Lys	Lys	Ala	Phe	Tyr	Asp	Asp
				180					185					190		
25	Asn	Arg	Pro	Ile	Glu	Tyr	Gly	Val	His	Ser	Lys	Asp	Glu			
		195						200					205			
	<210>	22														
	<211>	510														
30	<212>	PRT														
	<213>	Staphylococcus aureus														
	<400>	22														
35	Asp	His	Tyr	Val	Ile	Gln	Tyr	Phe	Ser	Gly	Leu	Ile	Gly	Gly	Arg	Gly
	1				5					10					15	
	Arg	Arg	Ala	Asn	Leu	Tyr	Gly	Leu	Phe	Asn	Lys	Ala	Ile	Glu	Phe	Glu
				20					25					30		
40	Asn	Ser	Ser	Phe	Arg	Gly	Leu	Tyr	Gln	Phe	Ile	Arg	Phe	Ile	Asp	Glu
			35				40						45			
	Leu	Ile	Glu	Arg	Gly	Lys	Asp	Phe	Gly	Glu	Glu	Asn	Val	Val	Gly	Pro
		50					55					60				
45	Asn	Asp	Asn	Val	Val	Arg	Met	Met	Thr	Ile	His	Ser	Ser	Lys	Gly	Leu
	65					70					75					80
	Glu	Phe	Pro	Phe	Val	Ile	Tyr	Ser	Gly	Leu	Ser	Lys	Asp	Phe	Asn	Lys
50					85					90					95	
	Arg	Asp	Leu	Lys	Gln	Pro	Val	Ile	Leu	Asn	Gln	Gln	Phe	Gly	Leu	Gly
			100						105					110		
55	Met	Asp	Tyr	Phe	Asp	Val	Asp	Lys	Glu	Met	Ala	Phe	Pro	Ser	Leu	Ala
		115						120					125			
	Ser	Val	Ala	Tyr	Arg	Ala	Val	Ala	Glu	Lys	Glu	Leu	Val	Ser	Glu	Glu
		130					135					140				
60	Met	Arg	Leu	Val	Tyr	Val	Ala	Leu	Thr	Arg	Ala	Lys	Glu	Gln	Leu	Tyr
	145					150					155					160

Leu Ile Gly Arg Val Lys Asn Asp Lys Ser Leu Leu Glu Leu Glu Gln
 165 170 175
 5 Leu Ser Ile Ser Gly Glu His Ile Ala Val Asn Glu Arg Leu Thr Ser
 180 185 190
 Pro Asn Pro Phe His Leu Ile Tyr Ser Ile Leu Ser Lys His Gln Ser
 195 200 205
 10 Ala Ser Ile Pro Asp Asp Leu Lys Phe Glu Lys Asp Ile Ala Gln Ile
 210 215 220
 Glu Asp Ser Ser Arg Pro Asn Val Asn Ile Ser Ile Val Tyr Phe Glu
 225 230 235 240
 15 Asp Val Ser Thr Glu Thr Ile Leu Asp Asn Asp Glu Tyr Arg Ser Val
 245 250 255
 Asn Gln Leu Glu Thr Met Gln Asn Gly Asn Glu Asp Val Lys Ala Gln
 260 265 270
 20 Ile Lys His Gln Leu Asp Tyr Arg Tyr Pro Tyr Val Asn Asp Thr Lys
 275 280 285
 25 Lys Pro Ser Lys Gln Ser Val Ser Glu Leu Lys Arg Gln Tyr Glu Thr
 290 295 300
 Glu Glu Ser Gly Thr Ser Tyr Glu Arg Val Arg Gln Tyr Arg Ile Gly
 305 310 315 320
 30 Phe Ser Thr Tyr Glu Arg Pro Lys Phe Leu Ser Glu Gln Gly Lys Arg
 325 330 335
 Lys Ala Asn Glu Ile Gly Thr Leu Met His Thr Val Met Gln His Leu
 340 345 350
 35 Pro Phe Lys Lys Glu Arg Ile Ser Glu Val Glu Leu His Gln Tyr Ile
 355 360 365
 40 Asp Gly Leu Ile Asp Lys His Ile Ile Glu Ala Asp Ala Lys Lys Asp
 370 375 380
 Ile Arg Met Asp Glu Ile Met Thr Phe Ile Asn Ser Glu Leu Tyr Ser
 385 390 395 400
 45 Ile Ile Ala Glu Ala Glu Gln Val Tyr Arg Glu Leu Pro Phe Val Val
 405 410 415
 Asn Gln Ala Leu Val Asp Gln Leu Pro Gln Gly Asp Glu Asp Val Ser
 420 425 430
 Ile Ile Gln Gly Met Ile Asp Leu Ile Phe Val Lys Asp Gly Val His
 435 440 445
 55 Tyr Phe Val Asp Tyr Lys Thr Asp Ala Phe Asn Arg Arg Arg Gly Met
 450 455 460
 Thr Asp Glu Glu Ile Gly Thr Gln Leu Lys Asn Lys Tyr Lys Ile Gln
 465 470 475 480
 60 Met Lys Tyr Tyr Gln Asn Thr Leu Gln Thr Ile Leu Asn Lys Glu Val
 485 490 495

Lys Gly Tyr Leu Tyr Phe Phe Lys Phe Gly Thr Leu Gln Leu
 500 505 510

5 <210> 23
 <211> 124
 <212> PRT
 <213> Staphylococcus aureus

10 <400> 23
 Met Lys Phe Leu Ser Phe Lys Tyr Asn Asp Lys Thr Ser Tyr Gly Val
 1 5 10 15

15 Lys Val Lys Arg Glu Asp Ala Val Trp Asp Leu Thr Gln Val Phe Ala
 20 25 30

Asp Phe Ala Glu Gly Asp Phe His Pro Lys Thr Leu Leu Ala Gly Leu
 35 40 45

20 Gln Gln Asn His Thr Leu Asp Phe Gln Glu Gln Val Arg Lys Ala Val
 50 55 60

Val Ala Ala Glu Asp Ser Gly Lys Ala Glu Asp Tyr Lys Ile Ser Phe
 65 70 75 80

25 Asn Asp Ile Glu Phe Leu Pro Pro Val Thr Pro Pro Asn Asn Val Ile
 85 90 95

30 Ala Phe Gly Arg Asn Tyr Lys Asp His Ala Asn Glu Leu Asn His Glu
 100 105 110

Val Glu Lys Leu Tyr Val Phe Thr Lys Ala Ala Ser
 115 120

35 <210> 24
 <211> 180
 <212> PRT
 <213> Staphylococcus aureus

40 <400> 24
 Ser Gly Thr Gly Phe Ile Val Gly Lys Asn Thr Ile Val Thr Asn Lys
 1 5 10 15

45 His Val Val Ala Gly Met Glu Ile Gly Ala His Ile Ile Ala His Pro
 20 25 30

Asn Gly Glu Tyr Asn Asn Gly Gly Phe Tyr Lys Val Lys Lys Ile Val
 35 40 45

50 Arg Tyr Ser Gly Gln Glu Asp Ile Ala Ile Leu His Val Glu Asp Lys
 50 55 60

55 Ala Val His Pro Lys Asn Arg Asn Phe Lys Asp Tyr Thr Gly Ile Leu
 65 70 75 80

Lys Ile Ala Ser Glu Ala Lys Glu Asn Glu Arg Ile Ser Ile Val Gly
 85 90 95

60 Tyr Pro Glu Pro Tyr Ile Asn Lys Phe Gln Met Tyr Glu Ser Thr Gly
 100 105 110

Lys Val Leu Ser Val Lys Gly Asn Met Ile Ile Thr Asp Ala Phe Val

115 120 125
 Glu Pro Gly Asn Ser Gly Ser Ala Val Phe Asn Ser Lys Tyr Glu Val
 130 135 140
 5 Val Gly Val His Phe Gly Gly Asn Gly Pro Gly Asn Lys Ser Thr Lys
 145 150 155 160
 10 Gly Tyr Gly Val Tyr Phe Ser Pro Glu Ile Lys Lys Phe Ile Ala Asp
 165 170 175
 Asn Thr Asp Lys
 180
 15 <210> 25
 <211> 239
 <212> PRT
 <213> Staphylococcus aureus
 20 <400> 25
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 1 5 10 15
 25 Thr Ser Ile Thr Gly Val Gly Thr Thr Met Val Glu Gly Ile Gln Gln
 20 25 30
 Thr Ala Lys Ala Glu Asn Thr Val Lys Gln Ile Thr Asn Thr Asn Val
 35 40 45
 30 Ala Pro Tyr Ser Gly Val Thr Trp Met Gly Ala Gly Thr Gly Phe Val
 50 55 60
 35 Val Gly Asn His Thr Ile Ile Thr Asn Lys His Val Thr Tyr His Met
 65 70 75 80
 Lys Val Gly Asp Glu Ile Lys Ala His Pro Asn Gly Phe Tyr Asn Asn
 85 90 95
 40 Gly Gly Gly Leu Tyr Lys Val Thr Lys Ile Val Asp Tyr Pro Gly Lys
 100 105 110
 Glu Asp Ile Ala Val Val Gln Val Glu Glu Lys Ser Thr Gln Pro Lys
 115 120 125
 45 Gly Arg Lys Phe Lys Asp Phe Thr Ser Lys Phe Asn Ile Ala Ser Glu
 130 135 140
 50 Ala Lys Glu Asn Glu Pro Ile Ser Val Ile Gly Tyr Pro Asn Pro Asn
 145 150 155 160
 Gly Asn Lys Leu Gln Met Tyr Glu Ser Thr Gly Lys Val Leu Ser Val
 165 170 175
 55 Asn Gly Asn Ile Val Ser Ser Asp Ala Ile Ile Gln Pro Gly Ser Ser
 180 185 190
 Gly Ser Pro Ile Leu Asn Ser Lys His Glu Ala Ile Gly Val Ile Tyr
 195 200 205
 60 Ala Gly Asn Lys Pro Ser Gly Glu Ser Thr Arg Gly Phe Ala Val Tyr
 210 215 220

Phe Ser Pro Glu Ile Lys Lys Phe Ile Ala Asp Asn Leu Asp Lys
 225 230 235

5 <210> 26
 <211> 470
 <212> PRT
 <213> Staphylococcus aureus

10 <400> 26
 Met Gly Cys Thr Val Lys Met Asn Lys Ile Asn Asp Arg Asp Leu Thr
 1 5 10 15

15 Glu Leu Ser Ser Tyr Trp Val Tyr Gln Asn Ile Asp Ile Lys Lys Glu
 20 25 30

Phe Lys Val Asn Gly Lys Arg Phe Lys Gln Val Asp Ser Tyr Asn Asp
 35 40 45

20 Asp Lys Asn Ser Asn Leu Asn Gly Ala Ala Asp Ile Lys Ile Tyr Glu
 50 55 60

Leu Leu Asp Asp Lys Ser Lys Pro Thr Gly Gln Gln Thr Ile Ile Tyr
 65 70 75 80

25 Gln Gly Thr Ser Asn Glu Ala Ile Asn Pro Asn Asn Pro Leu Lys Ser
 85 90 95

30 Ser Gly Phe Gly Asp Asp Trp Leu Gln Asn Ala Lys Leu Met Asn Asn
 100 105 110

Asp Asn Glu Ser Thr Asp Tyr Leu Lys Gln Thr Asp Gln Leu Ser Asn
 115 120 125

35 Gln Tyr Lys Ile Lys Leu Glu Asp Ala Asp Arg Leu Ser Asn Ser Asp
 130 135 140

Phe Leu Lys Lys Tyr Arg Met Glu Ser Ser Asn Phe Lys Asn Lys Thr
 145 150 155 160

40 Ile Val Ala Asp Gly Gly Asn Ser Glu Gly Gly Ala Gly Ala Lys Tyr
 165 170 175

Gln Gly Ala Lys His Pro Asn Glu Lys Val Val Ala Thr Asp Ser Ala
 180 185 190

Met Ile Pro Tyr Ala Ala Trp Gln Lys Phe Ala Arg Pro Arg Phe Asp
 195 200 205

50 Asn Met Ile Ser Phe Asn Ser Thr Asn Asp Leu Leu Thr Trp Leu Gln
 210 215 220

Asp Pro Phe Ile Lys Asp Met Pro Gly Lys Arg Val Asn Ile Asn Asp
 225 230 235 240

55 Gly Val Pro Arg Leu Asp Thr Leu Ile Asp Ser His Val Gly Tyr Lys
 245 250 255

Arg Lys Leu Asn Arg Lys Asp Asn Thr Tyr Asp Thr Val Pro Leu Ile
 260 265 270

60 Lys Ile Lys Ser Val Lys Asp Thr Glu Ile Lys Asn Gly Lys Lys Val
 275 280 285

Lys Lys Thr Ile Asn Ile Thr Leu Asp Met Asp Gly Arg Ile Pro Ile
 290 295 300
 5 Asn Val Trp Thr Gly Asp Ser Ile Ala Arg Ser Gly Arg Gly Thr Leu
 305 310 315 320
 Ile Lys Leu Asn Leu Glu Asn Leu Asp Ala Leu Ser Lys Leu Ile Thr
 325 330 335
 10 Gly Glu Thr Ser Gly Met Leu Ala Glu Cys Val Ile Phe Leu Asn Glu
 340 345 350
 Ser Phe Asn Ile Ser Glu Asn Glu Asn Lys Asn Phe Ala Asp Arg Lys
 355 360 365
 15 Lys Gln Leu Ser Glu Gly Phe Lys Asp Lys Ile Asn Leu Phe Gln Leu
 370 375 380
 20 Glu Glu Met Glu Arg Thr Leu Ile Ser Lys Ile Asn Ser Leu Glu Glu
 385 390 395 400
 Val Ala Asp Glu Thr Ile Glu Ser Ile Ser Ala Val Lys His Leu Leu
 405 410 415
 25 Pro Asp Phe Ala Leu Asp Ala Leu Lys Glu Arg Ile Asn Glu Leu Phe
 420 425 430
 30 Lys Gly Ile Lys Ser Phe Ile Glu Lys Val Tyr Asp Ser Ile Asp Asn
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 Gly Asp Lys Lys Leu Pro Ile Lys Leu Val Ser Tyr Asp Thr Val Lys
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 Asp Tyr Ala Tyr Ile Arg Phe Ser Val Ser Asn Gly Thr Lys Ala Val
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 60 Lys Ile Val Ser Ser Thr His Phe Asn Asn Lys Glu Glu Lys Tyr Asp
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 Tyr Thr Leu Met Glu Phe Ala Gln Pro Ile Tyr Asn Ser Ala Asp Lys

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	Phe Lys Thr Glu Glu Asp Tyr Lys Ala Glu Lys Leu Leu Ala Pro Tyr				
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5	Lys Lys Ala Lys Thr Leu Glu Arg Gln Val Tyr Glu Leu Asn Lys Ile				
	130		135		140
10	Gln Asp Lys Leu Pro Glu Lys Leu Lys Ala Glu Tyr Lys Lys Lys Leu				
	145		150		155
	Glu Asp Thr Lys Lys Ala Leu Asp Glu Gln Val Lys Ser Ala Ile Thr				
		165		170	175
15	Glu Phe Gln Asn Val Gln Pro Thr Asn Glu Lys Met Thr Asp Leu Gln				
		180		185	190
	Asp Thr Lys Tyr Val Val Tyr Glu Ser Val Glu Asn Asn Glu Ser Met				
		195		200	205
20	Met Asp Thr Phe Val Lys His Pro Ile Lys Thr Gly Met Leu Asn Gly				
		210		215	220
25	Lys Lys Tyr Met Val Met Glu Thr Thr Asn Asp Asp Tyr Trp Lys Asp				
		225		230	235
	Phe Met Val Glu Gly Gln Arg Val Arg Thr Ile Ser Lys Asp Ala Lys				
		245		250	255
30	Asn Asn Thr Arg Thr Ile Ile Phe Pro Tyr Val Glu Gly Lys Thr Leu				
		260		265	270
	Tyr Asp Ala Ile Val Lys Val His Val Lys Thr Ile Asp Tyr Asp Gly				
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		20		25	30
55	Val Ser Asn Val Ser Arg Thr Gly Asn Asn Ala Asn Val Thr Val Thr				
		35		40	45
	Val Thr Tyr Gln Asp Gly Thr Thr Ser Thr Val Thr Val Pro Val Lys				
		50		55	60
60	His Val Ile Pro Glu Ile Val Ala His Ser His Tyr Thr Val Gln Gly				
		65		70	75
					80

	Gln	Asp	Phe	Pro	Ala	Gly	Asn	Gly	Ser	Ser	Ala	Ser	Asp	Tyr	Phe	Lys
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5	Leu	Ser	Asn	Gly	Ser	Asp	Ile	Ala	Asp	Ala	Thr	Ile	Thr	Trp	Val	Ser
				100					105					110		
	Gly	Gln	Ala	Pro	Asn	Lys	Asp	Asn	Thr	Arg	Ile	Gly	Glu	Asp	Ile	Thr
			115					120					125			
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	Thr	Ala	Thr	Tyr	Lys	Val	Val	Arg	Thr	Val	Pro	Lys	His	Val	Phe	Glu
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	Thr	Ala	Arg	Gly	Val	Leu	Tyr	Pro	Gly	Val	Ser	Asp	Met	Tyr	Asp	Ala
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20	Lys	Gln	Tyr	Val	Ly's	Pro	Val	Asn	Asn	Ser	Trp	Ser	Thr	Asn	Ala	Gln
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	His	Met	Asn	Phe	Gln	Phe	Val	Gly	Thr	Tyr	Gly	Pro	Asn	Lys	Asp	Val
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25	Val	Gly	Ile	Ser	Thr	Arg	Leu	Ile	Arg	Val	Thr	Tyr	Asp	Asn	Arg	Gln
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	Thr	Glu	Asp	Leu	Thr	Ile	Leu	Ser	Lys	Val	Lys	Pro	Asp	Pro	Pro	Arg
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	Ile	Asp	Ala	Asn	Ser	Val	Thr	Tyr	Lys	Ala	Gly	Leu	Thr	Asn	Gln	Glu
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	Ala	Asp	Asn	Thr	Pro	Leu	Asn	Val	Thr	Asn	Ile	Thr	His	Gly	Ser	Gly
			275					280					285			
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		290					295					300				
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45		305				310					315					320
	Asp	Glu	His	Gly	Gln	Val	Val	Thr	Val	Thr	Arg	Asn	Glu	Ser	Val	Asp
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50	Ser	Asn	Asp	Ser	Ala	Thr	Val	Thr	Val	Thr	Pro	Gln	Leu	Gln	Ala	Thr
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	Thr	Glu	Gly	Ala	Val	Phe	Ile	Lys	Gly	Gly	Asp	Gly	Phe	Asp	Phe	Gly
			355					360					365			
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		370					375					380				
	Trp	His	Asp	Ser	Pro	Asp	Thr	Trp	Lys	Asn	Thr	Val	Gly	Asn	Thr	His
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	Lys	Thr	Ala	Val	Val	Thr	Leu	Pro	Asn	Gly	Gln	Gly	Thr	Arg	Asn	Val
					405					410					415	

Glu Val Pro Val Lys Val Tyr Pro Val Ala Asn Ala Lys Ala Pro Ser
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 5 Arg Asp Val Lys Gly Gln Asn Leu Thr Asn Gly Thr Asp Ala Met Asn
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 Tyr Ile Thr Phe Asp Pro Asn Thr Asn Thr Asn Gly Ile Thr Ala Ala
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 10 Trp Ala Asn Arg Gln Gln Pro Asn Asn Gln Gln Ala Gly Val Gln His
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 Leu Asn Val Asp Val Thr Tyr Pro Gly Ile Ser Ala Ala Lys Arg Val
 485 490 495
 15 Pro Val Thr Val Asn Val Tyr Gln Phe Glu Phe Pro Gln Thr Thr Tyr
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 20 Thr Thr Thr Val Gly Gly Thr Leu Ala Ser Gly Thr Gln Ala Ser Gly
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 Tyr Ala His Met Gln Asn Ala Thr Gly Leu Pro Thr Asp Gly Phe Thr
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 25 Tyr Lys Trp Asn Arg Asp Thr Thr Gly Thr Asn Asp Ala Asn Trp Ser
 545 550 555 560
 Ala Met Asn Lys Pro Asn Val Ala Lys Val Val Asn Ala Lys Tyr Asp
 565 570 575
 30 Val Ile Tyr Asn Gly His Thr Phe Ala Thr Ser Leu Pro Ala Lys Phe
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 Val Val Lys Asp Val Gln Pro Ala Lys Pro Thr Val Thr Glu Thr Ala
 595 600 605
 35 Ala Gly Ala Ile Thr Ile Ala Pro Gly Ala Asn Gln Thr Val Asn Thr
 610 615 620
 40 His Ala Gly Asn Val Thr Thr Tyr Ala Asp Lys Leu Val Ile Lys Arg
 625 630 635 640
 Asn Gly Asn Val Val Thr Thr Phe Thr Arg Arg Asn Asn Thr Ser Pro
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 45 Trp Val Lys Glu Ala Ser Ala Ala Thr Val Ala Gly Ile Ala Gly Thr
 660 665 670
 Asn Asn Gly Ile Thr Val Ala Ala Gly Thr Phe Asn Pro Ala Asp Thr
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 50 Ile Gln Val Val Ala Thr Gln Gly Ser Gly Glu Thr Val Ser Asp Glu
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 55 Gln Arg Ser Asp Asp Phe Thr Val Val Ala Pro Gln Pro Asn Gln Ala
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 5 Val Arg Gly Gln Asn Asn Gln Trp Thr Ile Ala Asn Lys Pro Asp Tyr
 770 775 780
 Val Thr Leu Asp Ala Gln Thr Gly Lys Val Thr Phe Asn Ala Asn Thr
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 10 Ile Lys Pro Asn Ser Ser Ile Thr Ile Thr Pro Lys Ala Gly Thr Gly
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 His Ser Val Ser Ser Asn Pro Ser Thr Leu Thr Ala Pro Ala Ala His
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 15 Thr Val Asn Thr Thr Glu Ile Val Lys Asp Tyr Gly Ser Asn Val Thr
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 25 Thr Thr Thr Ile Pro Val Thr Val Thr Tyr Asn Asp Gly Ser Thr Glu
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 Pro Gly Thr Ile Thr Gln Tyr Asn Asn Ala Met His Asn Ala Gln Gln
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 Gln Ile Asn Thr Ala Lys Thr Glu Ala Gln Gln Val Ile Asn Asn Glu
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 980 985 990
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 5 Tyr Asn Asn Ser Ile Arg Ala Leu Gln Ser Asp Leu Thr Ser Ala Lys
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 Lys Tyr Asn Ser Leu Lys Gln Ala Ile Ala Gly Leu Thr Pro Asp Leu
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Glu Gln Ser Ile Asn Gln Pro Thr Asp Thr Thr Gly Met Thr Thr Ala
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 10 Asn Asp Lys Val Thr Glu Ala Asn Gln Ala Lys Asp Gln Leu Asn Thr
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 15 His Gly Ala Ser Asn Leu Asn Gln Ala Gln Gln Asn Asn Phe Thr Gln
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 30 Val Ile Gly Glu Thr Thr Asn Pro Thr Met Asp Val Asn Thr Val Asn
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 10 Asp Gln Val Lys Arg Thr Glu Asp Tyr Ala Asp Ala Asp Thr Ala Lys
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 15 Gln Thr Thr Asn Pro Thr Met Ser Val Asp Asp Val Asn Arg Ala Thr
 1845 1850 1855
 Ser Ala Val Thr Ser Asn Lys Asn Ala Leu Asn Gly Tyr Glu Lys Leu
 1860 1865 1870
 Ala Gln Ser Lys Thr Asp Ala Ala Arg Ala Ile Asp Ala Leu Pro His
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 Ser Asn Ile Ala Gly Val Asn Thr Val Lys Gln Gln Gly Thr Asp Leu
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 30 Asn Thr Ala Met Gly Asn Leu Gln Gly Ala Ile Asn Asp Glu Gln Thr
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 40 Asn Gly Gln Asn Lys Thr Lys Asp Gln Val Thr Glu Ala Met Asn Gln
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 Val Asn Ser Ala Lys Asn Asn Leu Asp Gly Thr Arg Leu Leu Asp Gln
 1985 1990 1995 2000
 45 Ala Lys Gln Thr Ala Lys Gln Gln Leu Asn Asn Met Thr His Leu Thr
 2005 2010 2015
 Thr Ala Gln Lys Thr Asn Leu Thr Asn Gln Ile Asn Ser Gly Thr Thr
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Pro Glu Met Asn Pro Ser Thr Ile Thr Gln Lys Ala Glu Gln Val Asn
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 Ala Leu Asn Gly Thr Gln Asn Leu Asn Asn Ala Lys Gln Ala Ala Ile
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 60 Val Gln His Asn Ala Thr Glu Leu Asn Thr Ala Met Gly Thr Leu Lys
 2420 2425 2430

His Ala Ile Ala Asp Lys Thr Asn Thr Leu Ala Ser Ser Lys Tyr Val
 2435 2440 2445
 5 Asn Ala Asp Ser Thr Lys Gln Asn Ala Tyr Thr Thr Lys Val Thr Asn
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 10 Glu Val Thr Ala Ala Ala Asn Gln Val Asn Ser Ala Lys Gln Glu Leu
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 Thr Asn Gly Gln Ala Leu Asn Asn Ala Met Lys Gly Leu Arg Asp Ser
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 25 Ile Ala Asn Glu Thr Thr Val Lys Thr Ser Gln Asn Tyr Thr Asp Ala
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	Asp	Gln	Ile	Asp	Lys	Thr	Asn	Asn	Thr	Tyr	Arg	Gln	Thr	Ile	Tyr	Val	
	385					390					395					400	

Asn Pro Ser Gly Asp Asn Val Ile Ala Pro Val Leu Thr Gly Asn Leu
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 5 Lys Pro Asn Thr Asp Ser Asn Ala Leu Ile Asp Gln Gln Asn Thr Ser
 420 425 430
 Ile Lys Val Tyr Lys Val Asp Asn Ala Ala Asp Leu Ser Glu Ser Tyr
 435 440 445
 10 Phe Val Asn Pro Glu Asn Phe Glu Asp Val Thr Asn Ser Val Asn Ile
 450 455 460
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 Asp Thr Asp Asn Pro His Lys Ile Thr Asn Glu Arg Ile Lys Lys Glu
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<400> 31

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Ser Asn Ser Lys Lys Val Asp His Lys Ala Gly Val Arg Ile Thr Lys
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 15 Lys Lys Leu Gln Glu Asn Arg Met Ala Asp Val Ile Asp Gly Thr Asn
 290 295 300
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 305 310

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 01/02685

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C12N15/31 C12N15/63 G01N33/68 C07K14/31 A61K39/085
 C07K16/12 C12N5/12 A61K39/40

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C12N G01N C07K A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, EMBL, WPI Data, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	ARIFUR RAHMAN ET AL.: "Gamma-Hemolysin genes in the same family with LukF and lukS genes in methicillin resistant Staphylococcus aureus" BIOSCIENCE BIOTECHNOLOGY BIOCHEMISTRY., vol. 57, no. 7, 1993, pages 1234-1236, XP002177747 TOKYO JP the whole document	1-9, 18-48
A	WO 99 50418 A (NEUTEC PHARMA PLC) 7 October 1999 (1999-10-07) the whole document	1-9, 18-49

☐ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"Z" document member of the same patent family

Date of the actual completion of the international search

18 September 2001

Date of mailing of the international search report

19.11.2001

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
 NL - 2280 HV Rijswijk
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Authorized officer

MONTERO LOPEZ B.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB 01/02685

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 26-32 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Partially 1-9, 18-49

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/GB 01/02685

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: Partially 1-9, 18-49

Staphylococcus aureus antigen encoded by a DNA sequence of SEQ ID NO:1, DNA sequence and variants thereof; vectors and host cells comprising the same and their use for the production of the polypeptide; vaccine comprising the antigen and its use in immunisation; antibodies directed to the antigen and vectors and hybridoma cells for their production; use of the antibodies for the manufacture of a medicament; use of the polypeptides for preparing a hybridoma cell-line.

2. Claims: Partially 1-9, 18-49

Staphylococcus aureus antigen encoded by a DNA sequence of SEQ ID NO:2, DNA sequence and variants thereof; vectors and host cells comprising the same and their use for the production of the polypeptide; vaccine comprising the antigen and its use in immunisation; antibodies directed to the antigen and vectors and hybridoma cells for their production; use of the antibodies for the manufacture of a medicament; use of the polypeptides for preparing a hybridoma cell-line.

3. Claims: Partially 1-9, 19-46

Staphylococcus aureus antigen encoded by a DNA sequence of SEQ ID NO:3, DNA sequence and variants thereof; vectors and host cells comprising the same and their use for the production of the polypeptide; vaccine comprising the antigen and its use in immunisation; antibodies directed to the antigen and vectors and hybridoma cells for their production; use of the antibodies for the manufacture of a medicament; use of the polypeptides for preparing a hybridoma cell-line.

4. Claims: Partially 1-9, 19-46

Staphylococcus aureus antigen encoded by a DNA sequence of SEQ ID NO:4, DNA sequence and variants thereof; vectors and host cells comprising the same and their use for the production of the polypeptide; vaccine comprising the antigen and its use in immunisation; antibodies directed to the antigen and vectors and hybridoma cells for their production; use of the antibodies for the manufacture of a medicament; use of the polypeptides for preparing a hybridoma cell-line.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/GB 01/02685

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

5. Claims: Partially 1-9, 19-46

Staphylococcus aureus antigen encoded by a DNA sequence of SEQ ID NO:5, DNA sequence and variants thereof; vectors and host cells comprising the same and their use for the production of the polypeptide; vaccine comprising the antigen and its use in immunisation; antibodies directed to the antigen and vectors and hybridoma cells for their production; use of the antibodies for the manufacture of a medicament; use of the polypeptides for preparing a hybridoma cell-line.

6. Claims: Partially 1-9, 18-48

Staphylococcus aureus antigen encoded by a DNA sequence of SEQ ID NO:6, DNA sequence and variants thereof; vectors and host cells comprising the same and their use for the production of the polypeptide; vaccine comprising the antigen and its use in immunisation; antibodies directed to the antigen and vectors and hybridoma cells for their production; use of the antibodies for the manufacture of a medicament; use of the polypeptides for preparing a hybridoma cell-line.

7. Claims: Partially 1-9, 19-46

Staphylococcus aureus antigen encoded by a DNA sequence of SEQ ID NO:7, DNA sequence and variants thereof; vectors and host cells comprising the same and their use for the production of the polypeptide; vaccine comprising the antigen and its use in immunisation; antibodies directed to the antigen and vectors and hybridoma cells for their production; use of the antibodies for the manufacture of a medicament; use of the polypeptides for preparing a hybridoma cell-line.

8. Claims: Partially 1-9, 19-46

Staphylococcus aureus antigen encoded by a DNA sequence of SEQ ID NO:8, DNA sequence and variants thereof; vectors and host cells comprising the same and their use for the production of the polypeptide; vaccine comprising the antigen and its use in immunisation; antibodies directed to the antigen and vectors and hybridoma cells for their production; use of the antibodies for the manufacture of a medicament; use of the polypeptides for preparing a hybridoma cell-line.

9. Claims: Partially 1-9, 19-46

Staphylococcus aureus antigen encoded by a DNA sequence of

INTERNATIONAL SEARCH REPORT

International Application No. PCT/GB 01/02685

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

SEQ ID NO:9, DNA sequence and variants thereof; vectors and host cells comprising the same and their use for the production of the polypeptide; vaccine comprising the antigen and its use in immunisation; antibodies directed to the antigen and vectors and hybridoma cells for their production; use of the antibodies for the manufacture of a medicament; use of the polypeptides for preparing a hybridoma cell-line.

10. Claims: Partially 1-9, 18-48

Staphylococcus aureus antigen encoded by a DNA sequence of SEQ ID NO:10, DNA sequence and variants thereof; vectors and host cells comprising the same and their use for the production of the polypeptide; vaccine comprising the antigen and its use in immunisation; antibodies directed to the antigen and vectors and hybridoma cells for their production; use of the antibodies for the manufacture of a medicament; use of the polypeptides for preparing a hybridoma cell-line.

11. Claims: Partially 1-9, 18-48

Staphylococcus aureus antigen encoded by a DNA sequence of SEQ ID NO:11, DNA sequence and variants thereof; vectors and host cells comprising the same and their use for the production of the polypeptide; vaccine comprising the antigen and its use in immunisation; antibodies directed to the antigen and vectors and hybridoma cells for their production; use of the antibodies for the manufacture of a medicament; use of the polypeptides for preparing a hybridoma cell-line.

12. Claims: Partially 1-9, 19-46

Staphylococcus aureus antigen encoded by a DNA sequence of SEQ ID NO:12, DNA sequence and variants thereof; vectors and host cells comprising the same and their use for the production of the polypeptide; vaccine comprising the antigen and its use in immunisation; antibodies directed to the antigen and vectors and hybridoma cells for their production; use of the antibodies for the manufacture of a medicament; use of the polypeptides for preparing a hybridoma cell-line.

13. Claims: Partially 1-9, 19-46

Staphylococcus aureus antigen encoded by a DNA sequence of SEQ ID NO:13, DNA sequence and variants thereof; vectors and host cells comprising the same and their use for the production of the polypeptide; vaccine comprising the

INTERNATIONAL SEARCH REPORT

International Application No. PCT/GB 01/02685

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

antigen and its use in immunisation; antibodies directed to the antigen and vectors and hybridoma cells for their production; use of the antibodies for the manufacture of a medicament; use of the polypeptides for preparing a hybridoma cell-line.

14. Claims: 10-17, and partially 24-46

Method to identify antigenic polypeptides by transfecting a pathogenic organism gene library into a host cell and contacting the expressed polypeptides with autologous antisera from an animal infected with the pathogenic organism; polypeptides so obtained, vaccines comprising the antigenic polypeptides and use in immunisation; antibodies directed to the antigenic polypeptides and vectors and hybridoma cells for their production; use of the antibodies for the manufacture of a medicament.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 01/02685

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 9950418	A	07-10-1999	AU 3156699 A	18-10-1999
			EP 1068328 A1	17-01-2001
			WO 9950418 A1	07-10-1999

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